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Review

Acute Myocardial Infarction and Ischemic Stroke as Systemic Accelerators of Atherosclerotic Plaque Inflammation and Vulnerability

Jiang-ming Yu[1#], Yu-Xiao Liu[1#], Qin Li[2#], Jia-Bin Zong[1], Tuersun Aili[1], Xin-Ran Zhao[1], Bo Hu[1*], Jie-Hong Wu[1*]

[1]Department of Neurology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430022, China. [2]Department of Vascular Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430000, China.

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ABSTRACT: Acute ischemic cardio-cerebrovascular events are critical clinical emergencies characterized by sudden interruption of arterial blood supply to the myocardium or cerebral tissue, predominantly presenting as acute myocardial infarction and ischemic stroke. Individuals affected by these events exhibit a significantly elevated risk of recurrence, particularly during the critical timeframe spanning the initial weeks to months following the primary incident. Accumulating evidence reveals that, in the aftermath of acute ischemic events, endothelial senescence and sustained endothelial dysfunction are mediated by trained immunity, alongside signaling cascades activated by exosome-derived ligands and neutrophil extracellular trap (NET)-derived cell-free DNA—most notably encompassing the Notch1 pathway and the high mobility group box 1–receptor for advanced glycation end products (HMGB1-RAGE) axis. Furthermore, neuroendocrine responses coupled with glucose metabolic dysregulation contribute to systemic inflammation and promote atherosclerotic progression. Current preclinical models highlight the therapeutic efficacy of multifaceted interventions, ranging from targeted interventions and immunomodulation to chemokine-receptor blockade. Consequently, this review elucidates the underlying mechanisms promoting post-ischemic plaque destabilization and systematically evaluates therapeutic strategies designed to minimize recurrence and optimize long-term patient outcomes.

Keywords: Acute ischemic cardio-cerebrovascular events, Atherosclerosis progression, Immunity, Neuroendocrine Regulation, Exosomes

Background

Acute ischemic events are characterized by the rapid onset of ischemia and subsequent tissue damage resulting from an abrupt interruption of blood flow, typically induced by vascular occlusion due to a thrombus or embolus [1, 2]. These events represent a leading cause of mortality in industrialized nations, predominantly presenting as myocardial infarction (MI) and ischemic stroke [3–5]. Atherosclerosis serves as the fundamental pathological basis underlying both conditions [6]. Atherosclerotic plaques, which form locally within the vascular wall, may undergo rupture, thereby triggering secondary thrombosis that occludes the vessel lumen and precipitates an acute ischemic event [7–10]. Within the coronary circulation, this process culminates in MI, whereas ischemic stroke ensues within the cerebral circulation [11, 12]. Although the definitive role of atherosclerosis in the onset of acute ischemic events is extensively established, recent studies increasingly emphasize that biological responses triggered by MI and ischemic stroke—namely, immune cell infiltration, activation of immune signaling pathways, epigenetic alterations, and exosome release—may actively exacerbate atherosclerotic plaque progression [7, 9, 13–16]. Pathologically and clinically, this accelerated

***Correspondence should be addressed to:** Dr. Jie-Hong Wu (Email: wujiehong@mail.hust.edu.cn) and Dr. Bo Hu (Email: hubo@mail.hust.edu.cn), Department of Neurology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430022, China. #These authors contributed equally to this work.

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progression manifests as an expansion in plaque volume and lipid core enlargement, thinning of the fibrous cap, intensified inflammatory cell infiltration, endothelial senescence, and heightened susceptibility to thrombosis or recurrent ischemic events. Importantly, these underlying mechanisms appear to function similarly in both conditions [14, 15]. Consequently, MI and ischemic stroke represent not merely the immediate sequelae of acute ischemic events, but may also actively promote the subsequent progression of atherosclerosis via multiple pathways [14, 17]. Therefore, a comprehensive elucidation of the mechanisms driving accelerated plaque progression following acute ischemic events, alongside the potential interplay between MI and ischemic stroke in promoting plaque destabilization, may uncover novel mechanisms or triggers essential for atherosclerosis advancement.

Table 1. Epidemiological Characteristics of Recurrent Myocardial Infarction (MI) and Stroke.

Study/Author	Study Population	Sample Size	Follow-up Duration	Key Metrics	Ref.
Uzuner, Nevzat; Uzuner, Gulnur Tekgol (2023)	Ischemic stroke patients from a single-center stroke registry	927 patients	9 years post first-ever stroke	Single stroke recurrence in 185 patients (20%) Multiple stroke recurrences in 32 patients (3.5%) Mean time to first recurrence: 1 year Mean time to multiple recurrences: 3 years Significant risk factors: congestive heart disease ($P < 0.015$) and diabetes mellitus ($P < 0.006$)	[186]
Kan et al. (2023)	Patients with acute ischemic stroke enrolled in 17 randomized controlled trials (RCTs)	6,392 patients (RIC group: 3,185; Control group: 3,207)	Outcome assessments at endpoints (including 90-day outcomes)	Chronic RIC reduced the recurrence of ischemic stroke at the endpoint (OR 0.67, 95% CI [0.51, 0.87]) Improved prognosis measured by mRS at 90 days (mRS 0–1: OR 1.29, 95% CI [1.09, 1.52]; mRS 0–2: OR 1.22, 95% CI [1.01, 1.48]) and by NIHSS score (MD −0.99, 95% CI [−1.45, −0.53]) No increase in adverse events such as death, intracerebral hemorrhage, pneumonia, or TIA, but a significant rise in benign RIC-related events (OR 26.79, 95% CI [12.08, 59.38])	[187]
Mohan et al. (2009)	First-ever stroke patients from a population-based South London Stroke Register	2,874 patients; 8,311 person-years	Mean of 2.9 years (cumulative risks reported up to 10 years)	Cumulative recurrence: 7.1% at 1 year, 16.2% at 5 years, and 24.5% at 10 years. Predictors at 1 year: prior MI (HR 1.73, 95% CI 1.08–2.78) and atrial fibrillation (HR 1.61, 95% CI 1.04–4.27). At 5 years: hypertension (HR 1.47, 95% CI 1.08–1.99) and atrial fibrillation (HR 1.79, 95% CI 1.29–2.49). At 10 years: older age ($p = 0.04$), hypertension (HR 1.38, 95% CI 1.04–1.82), prior MI (HR 1.50, 95% CI 1.06–2.11), and atrial fibrillation (HR 1.51, 95% CI 1.09–2.09)	[19]

Abbreviations: MI, myocardial infarction; OR, odds ratio; CI, confidence interval; HR, hazard ratio; RIC, remote ischemic conditioning; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack.

Epidemiology

Following an initial acute ischemic event, the risk of subsequent cardiovascular events, notably stroke and MI, remains markedly elevated [18, 19]. In a large-scale national registry study from Sweden, Jernberg et al. reported that 18.3% of MI patients experienced recurrent MI, stroke, or cardiovascular-related death within one year of the index event; among these recurrences, 55.5% were non-fatal MI, 13.4% were non-fatal strokes, and 31.0% resulted in cardiovascular mortality [20]. In another investigation involving 10,599 MI patients from the VALIANT trial cohort, Thune et al. documented that 861 patients (9.6%) experienced recurrent MI over a mean follow-up period of 27.4 months, with a median recurrence time of 136 days (interquartile range: 35–361 days). Notably, the 7-day mortality rate following recurrent MI was significantly elevated at 20.5% [21]. Similarly, Burn et al. examined 180 recurrent stroke cases within an Oxfordshire community, revealing a 5-year

stroke recurrence risk of 30%, approximately nine-fold higher than that of the general population [22]. Furthermore, Cabral et al. investigated 399 stroke patients in Joinville, Brazil, observing a 1% stroke recurrence rate within the initial month, alongside cumulative recurrence risks of 6% at one year and 12% at five years—figures comparable to those reported in North Manhattan (1.5%) and South London (1.1%) [23]. To evaluate stroke recurrence rates, underlying etiology, and mortality within three months of the initial event, Liu et al. analyzed pooled data from over 10,000 patients enrolled in the Third Chinese National Stroke Registry; this analysis reported recurrence rates of 9.7% for large-artery atherosclerosis, 7.8% for cardiogenic embolism, and 4.5% for small-vessel occlusion [24]. Consequently, the recurrence of MI or stroke following an acute ischemic event represents a highly frequent clinical occurrence (Table 1). Nevertheless, the available literature predominantly relies on clinical endpoints—namely, recurrent MI and stroke—providing limited information regarding direct morphological alterations in atherosclerotic plaques preceding and succeeding the index event. Moreover, the recurrence of clinical events is inherently confounded by multiple unmeasured variables that prove challenging to fully disentangle. Specifically, such recurrent events may merely reflect residual plaque burden, atrial fibrillation, embolic sources, uncontrolled risk factors, medication adherence, or comorbidities, rather than constituting a direct consequence of the index event. Collectively, current epidemiological evidence is restricted to establishing a correlative association between acute ischemic events and long-term recurrence risk, rather than elucidating definitive causality.

Endothelial dysfunction and coagulation abnormalities

Endothelial dysfunction and coagulation abnormalities are central to the rapid progression of atherosclerotic plaques following MI [25, 26]. This concept is supported by research from Ozawa et al., wherein a hyperlipidemic mouse model ($LDLR^{-/-}Apobec1^{-/-}$) was subjected to closed-chest MI. Molecular imaging via contrast-enhanced ultrasound (CEUS) revealed a two- to four-fold increase in endothelium-associated von Willebrand factor (VWF) signaling. Additionally, at three and twenty-one days post-aortic constriction, the expression levels of P-selectin, vascular cell adhesion molecule (VCAM)-1, and platelet membrane glycoprotein Ibα (GPIbα) were elevated two- to four-fold in MI mice relative to sham controls, indicative of substantial endothelial activation and heightened platelet adhesion [27, 28]. Histological examination of the aortic root in MI mice demonstrated a two- to four-fold enlargement in plaque dimensions, augmented macrophage infiltration, a 20-fold surge in platelet adhesion, and upregulated platelet-derived transforming growth factor-beta 1 (TGFβ1) signaling markers [29].

As elucidated in a murine MI model, VWF interacts with the platelet GPIbα receptor to promote platelet adhesion and activation, while concurrently engaging the TGFβ1 signaling pathway and prompting the release of matrix metalloproteinase (MMP)-9, which collectively destabilize the fibrous cap of atherosclerotic plaques [30–35]. Furthermore, *in vitro* investigations utilizing human cells have demonstrated that an augmented oxidative stress environment induces the upregulation of the glycolytic enzyme fructose-2,6-bisphosphatase 3 (PFKFB3), thereby exacerbating endothelial injury, enhancing glucose metabolism, and amplifying the expression of proinflammatory mediators, including intercellular adhesion molecule (ICAM)-1 and VCAM-1 [36, 37]. This escalation in leukocyte adhesion and vascular inflammation is further compounded by metabolic reprogramming, which disrupts endothelial barrier integrity and elevates reactive oxygen species (ROS) production; consequently, this intensifies intraplaque lipid oxidation and creates a prothrombotic microenvironment [37–39].

Therapeutic interventions targeting VWF—specifically, the chronic administration of recombinant ADAMTS13 (rADAMTS13) and oral N-acetylcysteine (NAC) in $LDLR^{-/-}Apobec1^{-/-}$ mice post-MI—yielded significant reductions in both molecular imaging signals and adverse plaque characteristics by attenuating endothelial VWF via proteolytic cleavage and disulfide bond reduction, respectively [40]. In contrast, factor XI inhibition exerted negligible effects. Collectively, these findings indicate that acute MI precipitates a prothrombotic milieu distinguished by elevated VWF and adhesion molecule expression on the endothelium, thereby potentiating platelet adhesion and driving plaque inflammation and expansion at distant vascular sites (Fig. 1) [29].

Despite a substantial elevation in endothelial cells (ECs) turnover within vulnerable regions of atherosclerotic plaques, the regenerative capacity remains markedly limited. Massa et al. conducted an extensive phenotypic and functional characterization of circulating $CD34^{+}$ progenitor cells derived from patients with acute MI [41, 42]. Their investigation revealed a pronounced, spontaneous surge in circulating hematopoietic and endothelial progenitor cells (EPCs), peaking within hours of symptom onset in acute MI [41]. Further investigations employing an ApoE-deficient murine model demonstrated that the heightened EC turnover adjacent to atherosclerotic plaques leads to EPC exhaustion and progressive functional impairment of EPCs.

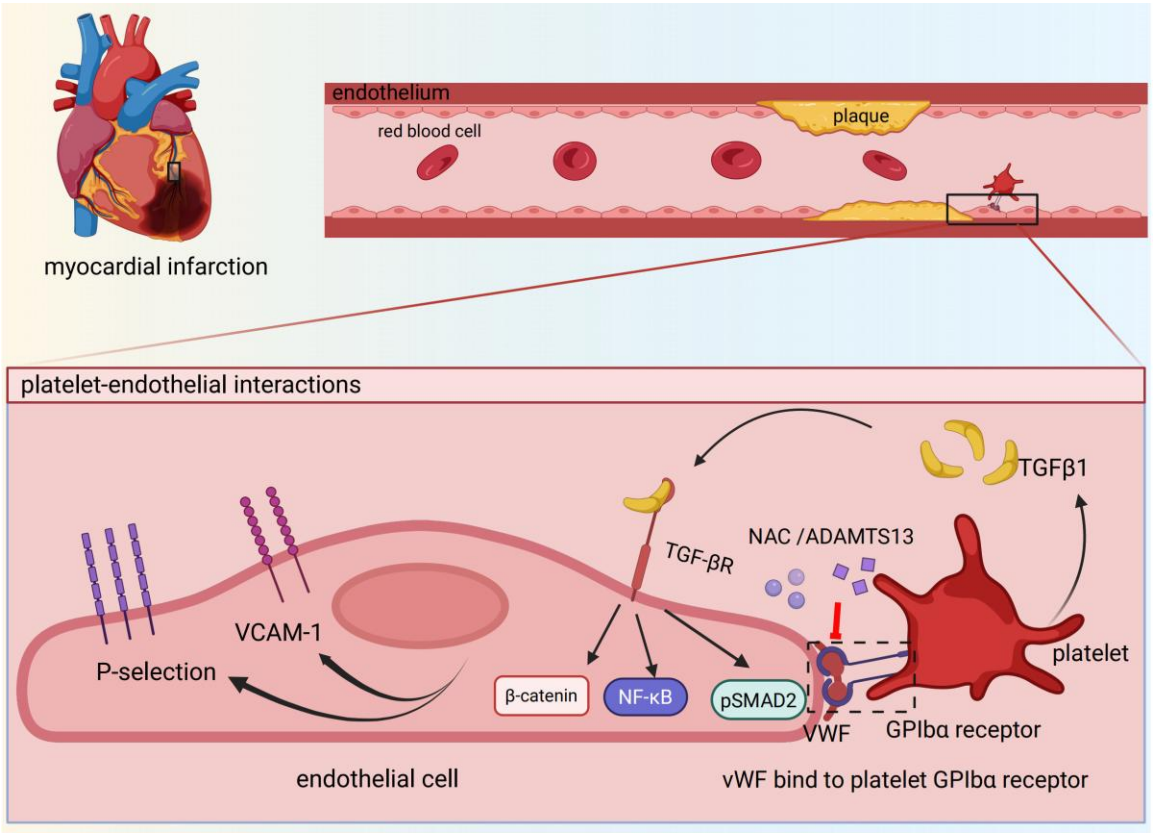


Figure 1. Schematic illustration of the molecular mechanisms underlying platelet-EC interactions following myocardial infarction. In mouse models, myocardial infarction leads to elevated levels of VWF in the circulation. VWF, serving as a molecular bridge, binds to ECs on one end and to the platelet GPIbα receptor on the other, thereby mediating platelet adhesion—a process that can be inhibited by NAC/ADAMTS13. Following platelet activation, released TGF-β1 binds to the TGF-β receptor on ECs, activating intracellular signal transduction. Key signaling molecules involved in this pathway, including pSMAD2, β-catenin, and NF-κB, are indicated in the diagram. These pathways may collectively upregulate the expression of VCAM-1 and P-selectin on ECs. Abbreviations: VWF: von Willebrand factor; GPIbα: membrane glycoprotein Ibα; NAC: N-acetylcysteine; ADAMTS13: a disintegrin and metalloproteinase with thrombospondin type 1 motifs, member 13; TGF-β1: transforming growth factor-beta 1; NF-κB: nuclear factor kappa B; VCAM-1: vascular cell adhesion molecule-1.

Under physiological conditions, EPCs migrate to sites of vascular injury, where they differentiate into mature ECs and secrete reparative factors, including vascular endothelial growth factor (VEGF) [43, 44]. However, within the pathophysiological milieu of atherosclerosis, hyperlipidemia and chronic inflammation deplete EPC reserves and compromise their functional integrity, as evidenced by attenuated migratory capacity and diminished secretion of pro-angiogenic cytokines. Following MI, the systemic inflammatory cascade further undermines EPC survival and differentiation, culminating in delayed endothelial repair that is disproportionate to the magnitude of injury [45]. This regenerative delay amplifies the susceptibility to endothelial denudation at the plaque surface, thereby facilitating thrombus formation in patients with coronary artery disease [43, 46, 47]. Consequently, while atherosclerosis accelerates EC turnover, insufficient or aberrant repair mechanisms compromise endothelial integrity, a process that potentially aggravates the atherosclerotic burden and predisposes individuals to further plaque development [26, 41, 43].

Furthermore, a parallel investigation employing a middle cerebral artery occlusion (MCAO) model alongside clinical specimens evaluated the systemic activation of vascular ECs following ischemic stroke and their consequent involvement in atherosclerotic progression [24, 48]. Observations from an ApoE$^{-/-}$ murine MCAO model indicated that ischemic stroke precipitates not only acute brain injury but also elicits a sustained inflammatory response within the ECs of large peripheral arteries [49, 50]. This response is characterized by the upregulation of VCAM-1 and an augmented expression of senescence markers—including P16, P53, and β-galactosidase—which persists for a minimum of four weeks [24, 51]. Collectively, these findings imply

that ischemic stroke extends beyond the induction of acute cerebral damage, instating large artery ECs in a protracted state of inflammation and senescence that potentially accelerates atherosclerotic development. To date, current evidence is largely restricted to clinical observations of enhanced EPC proliferation in patients with acute ischemic events, alongside animal models showing that acute ischemic events elevate VWF levels to promote peripheral atherosclerosis. Nevertheless, the precise mechanisms by which persistent endothelial inflammation and dysfunction following myocardial infarction drive atherosclerotic plaque progression remain poorly defined and warrant thorough investigation.

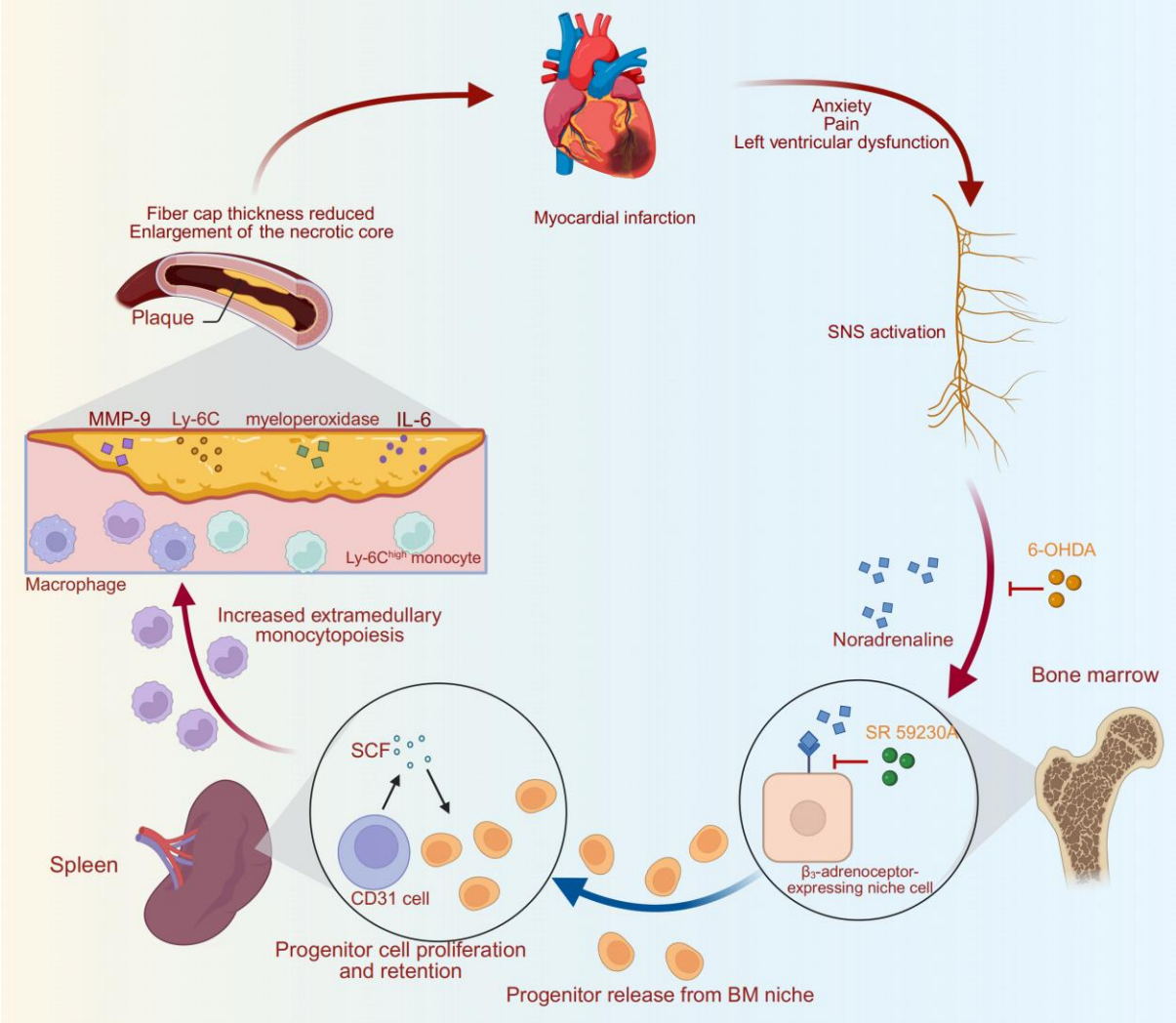


Figure 2. Myocardial infarction accelerates atherosclerosis through activation of the sympathetic nervous system. In mouse models of MI, MI-induced left ventricular dysfunction, along with associated pain and anxiety, activates the SNS. The activated SNS releases norepinephrine, a process that can be blocked by 6-OHDA. Norepinephrine acts on β3-adrenergic receptors expressed on bone marrow niche cells (e.g., $CD31^+$ cells), leading to the mobilization of HSPCs from their bone marrow niches into the circulation. SR 59230 can block this process. In mice, these mobilized progenitor cells enter the circulation and migrate to the spleen. Within the spleen, a newly formed niche, constituted by factors such as SCF produced by $CD31^+$ cells, supports the proliferation and retention of these progenitor cells, resulting in a substantial increase in extramedullary monocytopoiesis. The spleen subsequently generates large quantities of inflammatory monocytes (e.g., $Ly\text{-}6C^+$ monocytes) and macrophages, which enter the circulation and accelerate the formation of atherosclerotic plaques. These pathways may collectively elevate levels of various pro-inflammatory factors (e.g., IL-6, Ly-6C) and proteases (e.g., MMP-9, myeloperoxidase) within plaques, leading to fibrous cap thinning and necrotic core expansion, thereby increasing plaque vulnerability. Abbreviations: SNS: sympathetic nervous system; 6-OHDA: 6-hydroxydopamine; HSPCs: hematopoietic stem/progenitor cells; SCF: stem cell factor; Ly-6C: lymphocyte antigen 6 complex, locus C; IL: interleukin; MMP: matrix metalloproteinase.

Neuroendocrine Regulation

Following acute ischemic events, the neuroendocrine system significantly influences the progression of atherosclerosis [52]. Activation of the sympathetic nervous system (SNS) and the subsequent release of stress hormones substantially promote the remodeling of atherosclerotic lesions [27]. Following MI in mice, sympathetic stimulation accelerates the mobilization of hematopoietic stem cells from the bone marrow and spleen, resulting in increased circulating monocytes [53]. These monocytes infiltrate and accumulate in atherosclerotic plaques, driving plaque expansion and destabilization (Fig. 2) [54]. Freemantle et al. conducted a randomized controlled trial assessing the efficacy of β-blockers in both short-term MI management and long-term secondary prevention [55, 56]. In a cohort of 54,234 patients (10.1%), 5,477 patients, randomized to either the β-blocker or control group, died. Long-term trials showed a 23% reduction in mortality (95% confidence interval, 15% to 31%), while short-term trials indicated only a 4% reduction (-8% to 15%), confirming the effectiveness of β-blockers for long-term secondary prevention following MI [57]. Additionally, Roth et al. demonstrated that in ischemic stroke, the release of the alarmin high mobility group box 1 (HMGB1) activated monocytes and ECs through a receptor for advanced glycation end products (RAGE) -mediated signaling, exacerbating atherosclerotic plaques in mice [58]. Inhibition of β3-adrenoreceptors reduced monocyte egress from the bone marrow post-stroke, but had no effect on monocyte activation, vascular inflammation, or plaque progression, suggesting that the sympathetic stress response and inflammation triggered by brain-released alarmins collectively drive the progression of post-stroke atherosclerosis [48].

Norepinephrine plays an integral role in the neuroendocrine regulation of atherosclerotic plaque destabilization following acute ischemic events [27, 59]. Acute stress triggers a systemic response, leading to the local release of norepinephrine from sympathetic nerve fibers [60, 61]. This norepinephrine reaches ECs either by diffusion through adjacent tissue layers or via direct neural connections to the intima, activating alpha-adrenergic receptors [62, 63]. Receptor activation initiates signaling to medial smooth muscle cells, causing vasoconstriction and elevated blood pressure [64]. Additionally, norepinephrine upregulates the release of chemokines, including C-X-C motif chemokine ligand 1 (CXCL1) and C-C motif chemokine ligand 7 (CCL7), from ECs and enhances the expression of adhesion molecules such as ICAM-1 and VCAM-1 [62]. These factors promote leukocyte infiltration, particularly monocytes, thereby enhancing local inflammatory responses. In mouse models, the heightened endothelial activation not only promotes monocyte adhesion and infiltration but may also increase the instability of existing plaques, raising the risk of plaque rupture [65]. Under prolonged stress conditions, norepinephrine, as observed *in vitro*, further induces trained immunity in monocytes through the cyclic adenosine monophosphate-protein kinase A (cAMP-PKA) pathway, increasing glycolytic capacity and oxidative phosphorylation in macrophages, which sustains a prolonged proinflammatory state [66, 67]. This sustained inflammation represents a potential mechanism by which neuroendocrine stress contributes to accelerated atherosclerotic plaque progression. While randomized controlled trials have established the long-term efficacy of β-blocker therapy for secondary prevention following myocardial infarction, animal models demonstrate that alarmins such as HMGB1 activate ECs and monocytes, thereby driving vascular inflammation and plaque progression. Moreover, although norepinephrine upregulates adhesion molecule expression on ECs, its regulatory effects on monocytes remain controversial, necessitating further investigation to define its precise role following acute ischemic events.

Metabolic Dysregulation

Metabolic dysregulation and aberrant molecular regulation represent key mechanisms contributing to atherosclerosis progression [68, 69]. This process entails disturbances in glucose metabolism and exosome-mediated alterations in gene expression, which together amplify inflammatory responses and destabilize plaques [36, 70]. Hyperglycemia not only directly damages ECs but also accelerates atherosclerosis by inducing trained immunity, which alters the epigenetic landscape of immune cells [71]. The transcription factor Runt-related transcription factor 1 (RUNX1) is central to this process; in mouse models of hyperglycemia, its binding to target gene promoters is enhanced, promoting macrophage polarization towards a proinflammatory (M1) phenotype while concurrently suppressing genes associated with the anti-inflammatory (M2) phenotype [71, 72]. Notably, even after glycemic normalization, the RUNX1-mediated epigenetic memory persists, maintaining the proinflammatory macrophage characteristics and contributing to the ongoing progression of atherosclerotic lesions. This mechanism partially explains the prolonged elevated cardiovascular risk in diabetic patients despite glycemic control.

Following a stroke, circulating monocytes exhibit increased glycolysis and elevated levels of hexokinase 2 (HK2), a key glycolytic enzyme, which further enhances glycolytic flux through the interleukin (IL) -1β signaling pathway [73, 74]. The activation of high glycolytic

activity and HK2 is essential for microglia-mediated hypoxic neuroinflammation, thereby intensifying systemic inflammatory responses and promoting atherosclerotic progression. Stroke-induced upregulation of HK2 in monocytes has been shown to not only heighten monocyte activation but also facilitate their recruitment to the vascular endothelium via the C-C motif chemokine ligand 2 - C-C chemokine receptor type 2 (CCL2-CCR2) axis [73, 75]. Furthermore, the damage-associated molecular pattern protein HMGB1 promotes HK2 upregulation and vascular inflammation through p38-dependent stabilization of hypoxia-inducible factor-1α (HIF-1α), perpetuating the cycle of atherosclerosis and inflammation (Figure 3). The levels of HK2 in circulating monocytes are positively correlated with hs-C-reactive protein (CRP) and National Institutes of Health Stroke Scale (NIHSS) scores, reflecting a strong link between metabolic changes and clinical severity [75]. Therefore, acute ischemic stroke, marked by enhanced glycolysis, not only results in localized ischemic injury but also triggers systemic immune activation, further accelerating atherosclerosis and increasing the risk of recurrent ischemic events.

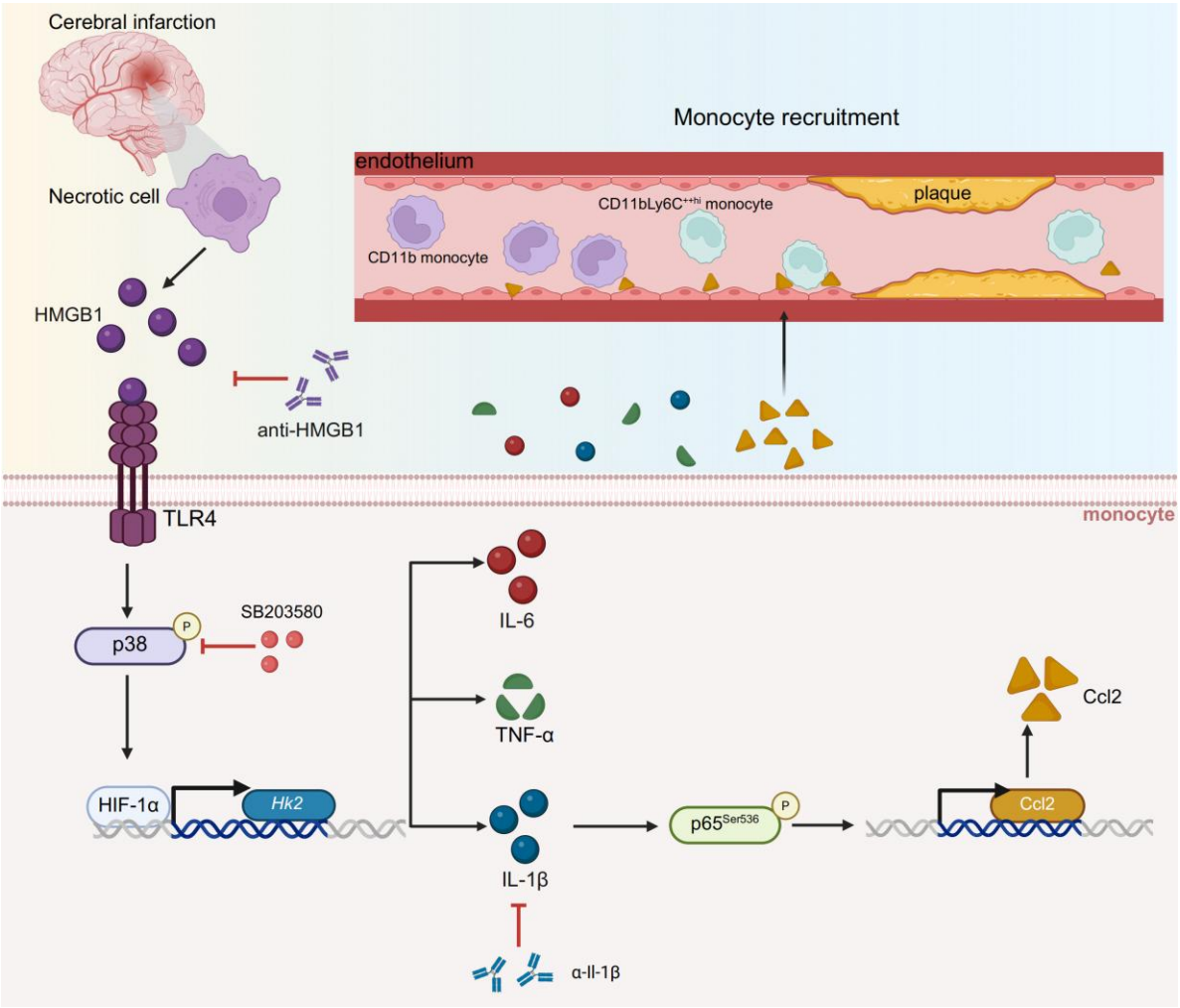


Figure 3. Mechanism of ischemic stroke -induced inflammation and monocyte recruitment. Ischemic stroke triggers cellular necrosis, leading to the release of HMGB1. In mouse models of ischemic stroke, HMGB1 binds to TLR4 on monocytes, an interaction that can be inhibited by anti-HMGB1 antibody. TLR4 activation subsequently phosphorylates and activates p38, a process that can be blocked by the p38 inhibitor SB203580. The activated p38 signaling pathway upregulates HIF-1α, which promotes the expression of HK2. Elevated HK2 expression facilitates the production of IL-6, TNF-α, and IL-1β. IL-1β induces the phosphorylation of p65Ser536 and upregulates the expression of CCL2. As demonstrated by animal evidence, the activity of IL-1β can be neutralized by an α-IL-1β inhibitor. Elevated CCL2 may recruit CD11b monocytes and CD11bLy6C++hi monocytes. Abbreviations: HMGB1: high-mobility group box 1; TLR4: Toll-like receptor 4; p38: p38 mitogen-activated protein kinase; HIF-1α: hypoxia-inducible factor-1α; HK2: hexokinase 2; IL: interleukin; TNF-α: tumor necrosis factor-α; p65Ser536: p65 at serine 536; CCL2: C-C motif chemokine ligand 2; Ly6C: lymphocyte antigen 6 complex, locus C.

Serum cholesterol efflux capacity (CEC) serves as a pivotal functional metric of the reverse cholesterol transport (RCT) pathway, providing prognostic insights that transcend static high-density lipoprotein cholesterol (HDL-C) levels [76]. Specifically, within the milieu of acute MI, CEC functions as an integrative biomarker that captures the systemic efficiency of cholesterol mobilization from atherosclerotic plaques. The clinical utility of this metric is underscored by data from a cohort of 1,609 consecutive patients with ST-segment elevation myocardial infarction (STEMI), where serum CEC demonstrated a robust inverse correlation with all-cause mortality; notably, patients in the highest CEC quartile exhibited a significantly reduced mortality risk compared to those in the lowest [77]. The human plasma-derived apolipoprotein A-I formulation CSL112 was developed as a targeted therapeutic strategy to counteract the compromised lipid functionality characteristic of this high-risk population. Upon infusion, CSL112 elicits a rapid and substantial augmentation of both total and ATP-binding cassette transporter A1-dependent CEC, effectively reinvigorating the RCT pathway during the vulnerable post-infarction window [78]. In summary, while intracellular HK2 levels in monocytes are correlated with disease severity in patients, current evidence confirming the pro-atherosclerotic role of HK2 remains confined to animal models, underscoring an unmet need for clinical investigations targeting HK2 inhibition.

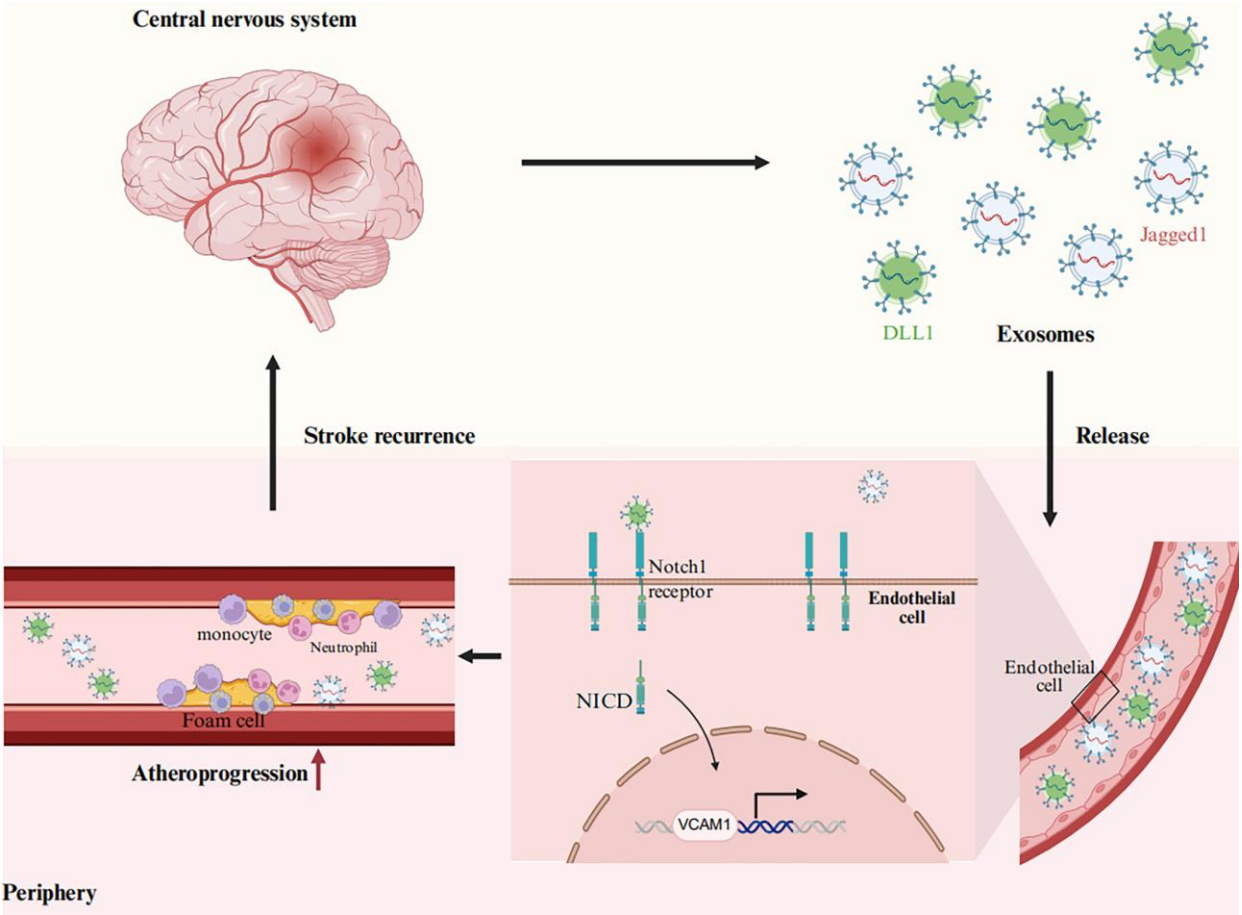


Figure 4. Exosome-mediated neurovascular crosstalk driving atheroprogression and stroke recurrence. Following ischemic stroke, single-cell sequencing and proteomics demonstrate that neurons and glia within the central nervous system release exosomes enriched in the Notch ligands DLL1 and Jagged1 into the circulation (top panel). These exosomes released by stroke model mice migrate to peripheral vascular endothelium (right panel), where DLL1 and Jagged1 bind Notch1 receptors on ECs, triggering proteolytic release of the NICD. NICD translocates to the nucleus to drive transcription of pro-adhesive genes such as VCAM-1 (inset panel). These pathways may collectively upregulate VCAM-1 expression, promoting the adhesion and transmigration of monocytes and neutrophils, increasing foam cell formation, and accelerating atherosclerotic plaque progression (lower left panel). Enhanced atheroprogression increases the risk of recurrent ischemic stroke, completing the vicious cycle of ischemic injury. Abbreviations: DLL1: delta-like ligand 1; NICD: Notch intracellular domain; VCAM: vascular cell adhesion molecule.

Exosomes-Mediated Pathways

Exosomes are nanoscale membrane-bound extracellular vesicles, ranging from 30 to 150 nm in diameter, originating from endosomal compartments across nearly all cell types [79]. These vesicles encapsulate a range of biomolecules, including proteins, lipids, and nucleic acids, which mirror the physiological or pathological state of the originating cell [80, 81]. In their capacity to transport bioactive molecules and modulate inflammatory responses, exosomes provide a valuable framework for investigating how endothelial activation following ischemia contributes to atherosclerotic plaque formation and elevates the risk of stroke recurrence.

The miR-186-5p/oxidized low-density lipoprotein receptor (LOX-1) axis plays a critical role in regulating lipid accumulation. In acute MI patients, a significant reduction in exosomal miR-186-5p levels disrupts its inhibitory effect on LOX-1, resulting in excessive uptake of oxidized low-density lipoprotein (oxLDL) by macrophages via the LOX-1 receptor and promoting foam cell formation [82, 83]. Animal studies further confirmed that exosomes from acute MI patients suppress miR-186-5p, leading to an expansion of necrotic core areas in plaques and an increase in atherosclerotic plaque area throughout the entire aorta [82, 83].

Additionally, a study integrated single-cell sequencing and proteomic microarray assays, demonstrating that brain tissue damage post-stroke can activate the Notch1 pathway in peripheral vascular ECs (Figure 4)[24]. This activation occurs via the sustained release of Notch1 receptor ligands delta-like ligand 1 (DLL1) and Jagged1 from exosomes, triggering vascular inflammation and accelerating atherosclerotic progression. Functional experiments demonstrated that inhibiting Notch1 or VCAM-1 significantly reduced endothelial activation, inflammatory cytokine expression, and adhesion of monocytes and neutrophils, either through specific antibodies or by genetic ablation of endothelial Notch1 [24, 84, 85]. Based on these results, the researchers proposed a novel strategy to predict post-stroke atherosclerosis progression by assessing DLL1 and Jagged1 levels in peripheral blood, alongside a new approach to slow this progression using immunologic interventions targeting the adhesion molecules VCAM-1 and Notch1 receptors. This intervention effectively slowed atherosclerotic progression, shedding light on the molecular mechanisms by which ischemic stroke-induced Notch1 activation contributes to systemic vascular dysfunction and subsequent plaque formation. Although patient blood profiling and multi-omics analyses support the association between exosomes and plaque progression following acute ischemic events, current sample sizes remain relatively small. Furthermore, the extreme complexity of exosomal cargo precludes the complete exclusion of synergistic or confounding effects from other molecules. Consequently, these findings necessitate further validation in larger human cohorts, alongside rigorous pathological tracking and mechanistic elucidation in animal models.

Systemic inflammatory response and immune activation in acute ischemic events

The role of systemic inflammatory response and immune activation in acute ischemic events has received increasing attention [86–88]. In particular, immune responses play a significant role in shaping clinical outcomes following MI and ischemic stroke (Figure 5) [89–91]. Joshi et al. conducted thoracic 18F-fluorodeoxyglucose positron emission tomography/computed tomography on 40 patients with MI and 40 with stable angina. Their study revealed that patients with ST-segment elevation MI had higher aortic 18F-fluorodeoxyglucose uptake, elevated plasma CRP levels, and larger infarct sizes compared to those with non-ST-segment elevation MI [92]. These data suggest that the extent of recurrent MI correlates with increased aortic atherosclerotic inflammation and a higher likelihood of early MI recurrence.

Pro-inflammatory factors exacerbate the systemic inflammatory response

Multiple studies have shown that during the post-MI recovery phase in murine models, necrotic cardiomyocytes release diverse endogenous signals—such as S100A1, S100A8/A9, HMGB1, galectin-3, S100β, and IL-1α—that initiate innate immune responses through the Toll-like receptor 4 (TLR4)/MyD88/NF-κB pathway [93–95]. TLR4 activation engages downstream mediators including MyD88 and NF-κB, driving the expression of a broad spectrum of inflammatory cytokines [96]. Once activated, NF-κB initiates a cascade characterized by the secretion of pro-inflammatory cytokines, notably tumor necrosis factor alpha (TNF-α), IL-1β, and IL-6 [97]. These cytokines not only enhance local immune activation but also exert systemic effects that contribute to atherosclerotic plaque expansion [2]. Notably, MyD88 deficiency has been associated with attenuated atherosclerosis, primarily through the suppression of vascular inflammation and oxidative stress [98]. In $ApoE^{-/-}$ mice, loss of MyD88 function results in a measurable decrease in aortic plaque burden [99].

Following MI, the inflammatory response is intensified, healing is impaired, and heart failure indicators worsen in mice deficient in Nr4a1 expression in hematopoietic cells [100]. Furthermore, the spleen

becomes the primary site for extramedullary hematopoiesis [53]. Nr4a1 has been identified as a key regulator of gene expression in macrophages [101]. Specifically, the nuclear hormone receptor Nr4a1 modulates both the early Ly-6Chigh monocyte-dominant inflammatory phase and the later Ly-6C low macrophage-dominant reparative phase within the infarcted myocardium [100].

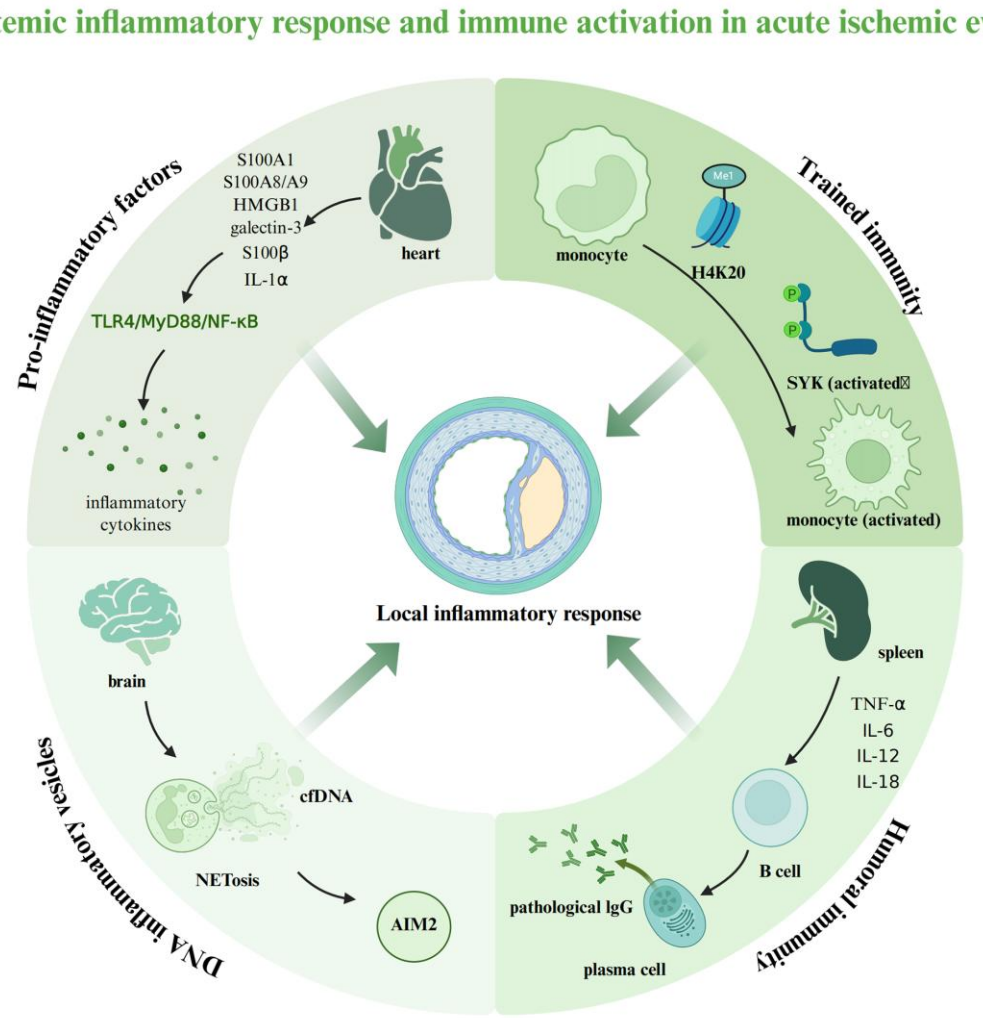


Figure 5. Systemic inflammatory response and immune activation in acute ischemic events. During the recovery phase in post-MI mice, damaged tissues release pro-inflammatory mediators that engage the TLR4/MyD88/NF-κB pathway in circulating leukocytes to drive inflammatory cytokine production (upper left quadrant). Following myocardial infarction in ApoE−/− mice, ischemia induces epigenetic reprogramming of monocytes—marked by H4K20 methylation and SYK phosphorylation—to establish trained immunity and heightened monocyte activation (upper right quadrant). Splenic B cells from post-MI ApoE−/− mice differentiate into plasma cells that secrete pathological IgG and pro-inflammatory cytokines (TNF-α, IL-6, IL-12, IL-18), amplifying humoral immune responses (lower right quadrant). In mouse models, ischemic stroke triggers neutrophil extracellular trap formation and release of cell-free DNA, which activates the AIM2 inflammasome in myeloid cells (lower left quadrant). These systemic immune and inflammatory signals may collectively converge on the vascular endothelium to potentiate the local inflammatory response within atherosclerotic lesions, accelerating plaque progression and increasing the risk of recurrent ischemic events. Abbreviations: IL: interleukin; TLR4: Toll-like receptor 4; MyD88: myeloid differentiation primary response 88; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; H4K20: histone H4 lysine 20; SYK: splenic tyrosine kinase; TNF-α: tumor necrosis factor-α; AIM2: absent in melanoma 2.

Additionally, cytokines such as granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-3 stimulate the proliferation and release of Ly-6C^{hi} monocytes [102]. These highly inflammatory monocytes migrate to atherosclerotic plaques via CCR2/C-X3-C motif chemokine receptor 1 (CX3CR1)-dependent chemotaxis and differentiate into pro-inflammatory M1 macrophages that secrete these cytokines, further aggravating local plaque inflammation [103, 104]. Additionally, hypercholesterolemia promotes the

expansion of Ly-6C^{hi} monocytes and their infiltration into plaques through the upregulation of endothelial adhesion molecules, including ICAM-1 and VCAM-1 [104]. Additionally, elevated levels of inflammatory markers, such as CRP, IL-6, and TNF-α, are closely linked to the accelerated progression of coronary artery disease, a relationship further supported by clinical studies [105].

Trained immunity to accelerate atherosclerotic plaque progression during MI

Trained immunity refers to a recently recognized phenomenon in which innate immune cells, traditionally regarded as lacking memory, undergo functional reprogramming following an initial exposure to a pathogen or stimulus [106]. This reprogramming enhances the nonspecific immune response during subsequent encounters with pathogens, even if they differ from the original stimulus [107]. In contrast to adaptive immunity, which depends on antigen-specific receptors and the clonal expansion of T and B lymphocytes, trained immunity is marked by a broad, cross-protective response predominantly mediated by cells such as monocytes, macrophages, and natural killer (NK) cells [108]. The molecular mechanisms driving trained immunity involve several key pathways. Pattern recognition receptors (PRRs), including TLRs, play a central role in detecting microbial components and initiating signaling cascades that lead to epigenetic modifications [109]. The resultant "memory" in innate immune cells is less specific than that of adaptive cells; rather, it induces a state of heightened readiness that provides protection against a broad range of pathogens [110]. This semi-specific memory is essential for host defense, particularly during the early stages of infection, before adaptive immune responses are fully activated.

Trained immunity plays a significant role in acute ischemic events [111, 112]. Zheng Dong et al. demonstrated that monocytes and macrophages underwent epigenetic changes following MI in ApoE$^{-/-}$ mice [14]. MI induces lysine methyltransferase 5A (KMT5A) upregulation via norepinephrine release from the sympathetic nervous system, which subsequently mediates the deposition of the histone H4 lysine 20 (H4K20) monomethylation modification in monocytes. This modification is concentrated in the SYK genomic region, contributing to its transcriptional activation. Simultaneously, the transcription factor CCHC-type zinc finger nucleic acid binding protein (CNBP) cooperates with KMT5A, leading to further upregulation of SYK expression and inducing a sustained pro-inflammatory phenotype to monocytes. Experimental data revealed that this MI-induced immune training was aggravated under high-fat diet or hyperlipidemia conditions, resulting in increased recruitment of inflammatory monocytes and macrophages to the vascular intima, thus promoting plaque formation and progression. Moreover, bone marrow transplantation experiments confirmed that MI-induced trained immunity can be transferred to uninjured mice, accelerating their atherosclerotic process [71]. Clinically, elevated SYK and KMT5A expression was observed in classical monocytes from patients with ST-segment elevation MI, which correlates with plaque progression [14]. Therefore, trained immunity triggered by MI during acute ischemic events enables monocytes to acquire a sustained proinflammatory phenotype through sympathetic-mediated synergistic activation of SYK via KMT5A and CNBP upregulation, thereby accelerating atherosclerotic plaque formation and progression.

Humoral immunity accelerates atherosclerosis after MI

Following MI, B cells contribute to atherosclerotic progression through the production of immunoglobulins [113]. In a study by Tin et al., an ApoE$^{-/-}$ mouse model was used in which MI was induced by ligation of the left coronary artery under high-fat diet conditions. After MI, the damaged myocardium released various alarm factors such as HMGB1, hsp60 (heat shock protein 60), and mtDNA (mitochondrial DNA）, which activated B cells via the TLR/MyD88 signaling pathway. Experimental data revealed that, in the spleens of mice post-MI, B cells rapidly upregulated multiple pro-humoral immune factors (e.g., TNF-α, IL-6, IL-12, and IL-18) and the chemokine receptor CCR7, promoting the migration of B cells to the T-cell zone border. This migration promoted further differentiation into antibody-producing plasma cells within the germinal center [114].

Following plasma cell differentiation, IgG accumulates in substantial amounts within established atherosclerotic plaques, where it interacts with Fcγ receptors on smooth muscle cells, macrophages, and NK/NKT cells, triggering local inflammatory responses that promote apoptosis and increase the size of necrotic nuclei, thus enhancing plaque instability [115]. To investigate this mechanism, B cells were depleted using anti-CD20 antibodies. The results revealed a significant reduction in IgG deposition, apoptotic cell count, and necrotic nucleus size in plaques after MI, with an effective suppression of plaque area expansion. In contrast, the transplantation of MI-activated B cells from the spleens of damaged mice into other ApoE$^{-/-}$ mice on a high-fat diet markedly aggravated plaque development, which was accompanied by elevated IgG deposition and intensified local inflammatory responses.

Additionally, plaque progression after MI was similarly inhibited by specific deletion of B lymphocyte-

induced maturation protein 1, a critical transcription factor involved in plasma cell differentiation in B cells, further confirming the role of antibody-dependent mechanisms in this process [116, 117]. Collectively, this study demonstrates that post-MI alarm signals activate B cells, promote plasma cell differentiation, and induce the production of pathological IgG, which mediate inflammation and apoptosis within localized plaques, accelerating the atherosclerotic process. These findings suggest novel therapeutic targets for preventing recurrent cardiovascular events after MI, such as inhibition of B-cell activation, plasma cell differentiation, or blockade of the TLR/MyD88 signaling pathway.

DNA inflammasome and acceleration of atherosclerotic process after ischemic stroke

Following an acute ischemic event, such as ischemic stroke, significant amounts of circulating free DNA (cfDNA) are released from damaged tissues, acting as key signaling molecules that activate DNA inflammasome [17, 118]. Research indicates that cfDNA is primarily derived from NET, a process rapidly triggered after stroke. DNA released through NETosis enters the bloodstream and promotes the formation of the absent in melanoma 2 (AIM2) inflammasome in atherosclerotic plaques, subsequently activating the effector enzyme caspase-1 [119]. This activation leads to the maturation and release of pro-inflammatory cytokines, including IL-1β, which intensify the local inflammatory microenvironment, enhancing plaque inflammation and maturation, and fostering the recruitment and proliferation of immune cells within the plaque [120, 121].

Subsequently, IL-1β induced a marked increase in the expression and activity of MMPs, particularly MMP2 and MMP9, within the plaque [122]. MMPs facilitated the degradation of the extracellular matrix, resulting in thinning of the fibrous cap and disorganization of collagen fibers, thereby destabilizing the plaque and rendering it more susceptible to rupture [123, 124]. Following plaque rupture, the risk of thrombosis and atheroembolism rises, ultimately precipitating secondary cerebral ischemic events or recurrent stroke.

These mechanisms have been demonstrated in animal models of experimental stroke or MI: acute ischemic events cause a transient elevation in cfDNA concentration, accompanied by increased caspase activity, IL-1β levels, and MMP activity within the plaque. These changes significantly heighten plaque vulnerability to rupture and thrombosis [17, 125–127]. Intervention studies revealed that neutralizing free DNA with DNase or using AIM2 inflammasome and caspase-1 inhibitors (e.g., VX765) effectively reduced intraplaque inflammation and MMP activity, thus lowering the incidence of recurrent ischemic events [128].

Furthermore, a significant increase in cfDNA, caspase-1 degradation products, MMP activity, and factor XIIa deposition in plaques from patients with acute stroke, compared to asymptomatic individuals, was observed in carotid endarterectomy samples [129]. In summary, the activation of AIM2 inflammasome plays a central role in accelerating atherosclerotic plaque progression following acute ischemic events, offering a potential therapeutic target for the prevention of early recurrent ischemic events. Although patient-derived circulating cfDNA and plaque specimens obtained via carotid endarterectomy have corroborated these underlying mechanisms, the extreme diversity of post-stroke damage-associated molecular patterns and their long-term impact on plaque progression remain poorly understood. Further clinical studies are needed to prove the therapeutic effects of the above targets.

Acute Ischemia, Inflammaging, and Vascular Aging

EPC dysfunction refers to a pathological phenomenon wherein EPCs undergo diverse environmental and cellular alterations with advancing age, leading to an accumulation of circulating senescent cells and compromised cellular function [130]. Accumulating evidence indicates that aging is accompanied by the upregulation of angiotensin II, which promotes ROS generation in early EPCs and accelerates cellular senescence, thereby underscoring the intrinsic link between aging and EPC dysfunction [131–133]. Comparative studies have demonstrated that, unlike young myocardial infarction patients, elderly patients exhibit significant deficits in EPC colony-forming, migratory, and vasculogenic capacities, with key functional properties—such as proliferation and migration—declining progressively with age [134–136]. Although acute ischemic events typically trigger a transient, rapid surge in circulating EPCs, whether aging-induced EPC impairment results in a loss of vascular protection and exacerbates the progression of atherosclerosis remains a critical question to be elucidated [41, 131, 137, 138]. Following myocardial infarction, local myocardial ischemia-reperfusion injury acts as a critical trigger for cellular senescence. This injury is accompanied by excessive ROS production, DNA damage, mitochondrial dysfunction, and exaggerated inflammatory responses; together, these pathological changes drive the premature senescence of cardiomyocytes, fibroblasts, and vascular ECs, along with the robust release of senescence-associated secretory phenotype (SASP) factors [139–141]. In rodent models of left anterior descending artery ligation followed by

reperfusion, progressive upregulation of cellular senescence markers that include senescence-associated β-galactosidase, p53, and p16 can be detected in peri-infarct tissues [139, 140]. At the vascular level, senescent ECs show impaired turnover and reduced exfoliation, which predisposes them to persist in the vascular wall; concurrently, the expression and activity of endothelial nitric oxide synthase are compromised, leading to insufficient nitric oxide bioavailability [142–144]. Furthermore, senescent ECs promote the progression of atherosclerosis through increased and sustained monocyte adhesion [145]. Collectively, these pathological alterations may represent a critical mechanism by which acute ischemic events accelerate atherosclerotic plaque progression.

Local ischemic injury is not confined to the heart; instead, it initiates a systemic pathological cascade. Inflammaging refers to the chronic, low-grade systemic inflammatory state that develops progressively with aging and represents a shared pathogenic pathway for cardiovascular and neurodegenerative diseases [14, 146, 147]. After myocardial infarction, transient stimulation by lipids and endogenous damage-associated molecular patterns induces long-term proinflammatory reprogramming in both mature innate immune cells and bone marrow hematopoietic progenitors [14, 50, 147]. This persistent inflammation triggered by a transient ischemic insult aligns closely with the core features of inflammaging, providing a potential explanation for how acute ischemic events promote systemic vascular aging and atherosclerotic progression. Immunosenescence—the progressive age-related structural and functional decline of the immune system—serves as a core driver of inflammaging [148]. In stroke patients, an aging-related skewing of B cells toward CD21-associated subsets may amplify harmful inflammatory and autoimmune responses following the event [149]. Similarly, in patients with MI, the immune system undergoes accelerated aging, characterized by lymphopenia, an expansion of terminally differentiated $CD8^+$ T lymphocytes, and heightened systemic inflammation [150, 151]. Furthermore, mitochondrial dysfunction in T cells and other lineages with advancing age promotes a senescent, cytotoxic phenotype in $CD8^+$ T cells, which accelerates systemic aging and drives pro-inflammatory cytokine-mediated premature aging in murine models [152–154]. Collectively, these pathways suggest that acute ischemic events may exacerbate immunosenescence, providing a compelling mechanism for accelerated atherosclerotic progression.

Clonal hematopoiesis of indeterminate potential (CHIP) is defined as the presence of somatic mutations associated with hematologic malignancies in peripheral blood or bone marrow cells, occurring in individuals who lack diagnostic criteria for hematologic disorders and present with normal blood cell counts [155]. Imbued with pro-inflammatory properties, CHIP-carrying immune cells—particularly macrophages and myeloid cells—accelerate plaque formation, necrosis, and vulnerability [156]. Amid acute ischemic events and systemic inflammation, CHIP emerges as an independent determinant of patient prognosis, wherein the interplay between stress-induced bone marrow mobilization and CHIP exacerbates plaque progression [157, 158]. Specifically, under stress conditions, hematopoietic stem cells carrying mutations in genes such as DNMT3A and TET2 gain a clonal expansion advantage and myeloid differentiation bias, preferentially generating large numbers of proinflammatory monocytes that are then released into the peripheral circulation. These mutant monocytes show upregulated expression of surface chemokine receptors and adhesion molecules, making them highly sensitive to chemotactic signals such as CCL2 released from atherosclerotic lesions, and thus significantly enhancing their transendothelial migratory capacity. After invading vascular wall lesions and differentiating into mutant macrophages, these cells exhibit hyperactivated intracellular inflammasomes and secrete abundant chemokines and proinflammatory cytokines, which in turn recruit more monocytes. This process forms a vicious feedback loop in the local vascular microenvironment, continuously driving the progression of atherosclerotic plaques [14, 147]. Preclinical evidence demonstrates that CHIP-related mutations exacerbate macrophage-mediated inflammation, characterized by heightened secretion of pro-inflammatory cytokines, notably IL-1β, IL-6, and TNF-α. Among these, TET2 mutations provoke particularly robust inflammatory surges, whereas ASXL1 mutations precipitate severe inflammatory phenotypes accompanied by metabolic reprogramming [159]. Efferocytosis—the specialized programmed clearance of apoptotic cells by phagocytes—is significantly compromised in senescent macrophages [160]. This functional defect results in the intralesional accumulation of apoptotic corpses, which subsequently aggravates plaque necrosis and vulnerability. The pathological cross-talk between macrophage senescence and necrosis establishes a self-amplifying positive feedback loop: impaired macrophage clearance intensifies local inflammation, which further drives necrosis and accelerates atherosclerotic progression [159]. Furthermore, bone marrow mobilization triggered by acute ischemic events may continuously feed this pool of efferocytosis-defective macrophages, culminating in advanced atherosclerotic plaque instability.

Aging is characterized by the progressive decline of cellular functions, which broadly impacts systemic

physiology through immune system dysregulation [161]. Clinical outcomes following acute ischemic events are strongly age-dependent, with this vulnerability significantly driven by age-related shifts in inflammatory dynamics [162–165].

Table 2. Mechanisms Driving Accelerated Atherosclerosis Following Myocardial Infarction and Ischemic Stroke.

Index Event	Systemic Trigger	Target Cell	Molecular Pathway	Plaque Effect	Evidence Type	Level of Translational Evidence	Therapeutic Implication	Ref.
MI	SNS	HSPCs	β_3R	Reduced fibrous cap thickness and enlarged necrotic cores	ApoE$^{-/-}$ mouse model of MI	Preclinical evidence	β-blockers reduce monocyte counts in ACS (retrospective evidence), consistent with murine models; targeted anti-inflammatory therapies have not been clinically translated.	[27]
MI	Systemic oxidative Stress	Platelet	VWF	Accelerated plaque growth and inflammatory activation	Mouse model of MI	Preclinical evidence	VWF-targeted therapies inhibit post-MI plaque acceleration and NF-κB-mediated inflammation in murine aortic atherosclerotic lesions.	[29]
MI	miR-186-5p	Macrophages	LOX-1	Marked increase in whole-aorta atherosclerotic plaque area	ApoE$^{-/-}$ mouse	Preclinical evidence	MiR-186-5p inhibits atherosclerosis-related macrophage phenotypes by regulating its downstream target LOX-1.	[82]
MI	Cardiac ischaemia and hyperlipidaemia	Monocyte	SYK/KMT5A	Enhanced formation of atherosclerotic plaques	ApoE$^{-/-}$ mouse model of MI	Early clinical evidence	Targeting epigenetics SYK/KMT5A inhibits monocyte pro-inflammatory phenotype, reducing post-MI plaque burden and cardiovascular event risk.	[14]
MI	Alarmins	B cells	TLR/MyD88	Increased lesion size, IgG accumulation, apoptotic cell count, and necrotic core expansion, promoting a more advanced and vulnerable plaque phenotype.	ApoE$^{-/-}$ mouse model of MI	Early clinical evidence	Targeting IRAK4 blocks the TLR-MyD88 pathway to suppress B-cell activation under clinical evaluation, and anti-CD20 B-cell depletion reduces atherosclerotic lesions.	[113, 169, 188]
MI	Systemic immune response	Endothelial cell	MCP-1/CCR2; CX3CL-1/CX3CR1	Increased plaque size and vulnerability, characterized by elevated pro-	ApoE$^{-/-}$ mouse model of MI	Preclinical evidence	StemBell treatment resulted in significantly increased cap thickness, decreased intra-plaque	[180]

				inflammatory monocyte infiltration			macrophage density, and elevated percentage of intra-plaque anti-inflammatory macrophages and chemokines, without affecting plaque size.	
Ischemic Stroke	HMGB1	Monocyte and EC	RAGE	Reduced fibrous cap thickness and increased number of highly unstable plaques	ApoE$^{-/-}$ mouse model of ischemic stroke	Preclinical evidence	Interfering with this sterile immune response by neutralizing brain-released alarmins may provide a therapeutic approach for stroke patients.	[48]
Ischemic Stroke	cfDNA	Macrophages	AIM2	Exacerbated inflammation, increased plaque vulnerability, thinning of the fibrous cap and extracellular matrix degradation	ApoE$^{-/-}$ mouse model of ischemic stroke	Preclinical evidence	The ReScinD trial (NCT05880524) evaluates DNase for stroke systemic inflammation, while 4-sulfonic calixarene AIM2 inhibition prevents post-stroke plaque activation and IL-1β elevation, outperforming NLRP3 inhibition by MCC950.	[17]
Ischemic Stroke	DLL1 and Jagged1	EC	Notch1	Acceleration of plaque growth, inflammation, and necrotic core	Mouse model of ischemic stroke	Preclinical evidence	Disruption of EC Notch1 signaling or VCAM1-mediated leukocyte adhesion suppresses these adverse systemic EC changes.	[24]
Ischemic Stroke	HMGB1	Monocyte	HK2	Increased plaque vulnerability, characterized by higher rupture rates, reduced fibrous cap thickness and collagen, and increased MMP2/MMP9 activity	ApoE$^{-/-}$ mouse model of ischemic stroke	Preclinical evidence	Targeting HK2, or upstream Hmgb1-driven p38-dependent Hif-1α stabilization, may represent an effective therapeutic strategy for atherosclerosis in stroke patients.	[73]

Abbreviations: MI, myocardial infarction; AIS, acute ischemic stroke; SNS, sympathetic nervous system; HSPCs, hematopoietic stem and progenitor cells; β3R, β3-adrenergic receptor; VWF, von Willebrand factor; NF-κB, nuclear factor kappa B; miR-186-5p, microRNA-186-5p; LOX-1, lectin-like oxidized low-density lipoprotein receptor-1; SYK, spleen tyrosine kinase; KMT5A, lysine methyltransferase 5A; TLR, Toll-like receptor; MyD88, myeloid differentiation primary response 88; IRAK4, interleukin-1 receptor-associated kinase 4; MCP-1, monocyte chemoattractant protein-1; CCR2, C-C chemokine receptor type 2; CX3CL1, C-X3-C motif chemokine ligand 1; CX3CR1, C-X3-C motif chemokine receptor 1; HMGB1, high mobility group box 1; RAGE, receptor for advanced glycation end products; cfDNA, circulating free DNA; AIM2, absent in melanoma 2; IL-1β, interleukin-1 beta; MMP, matrix metalloproteinase; DLL1, delta-like ligand 1; HK2, hexokinase 2; HIF-1α, hypoxia-inducible factor-1α.

Evidence from clinical cohorts of patients with STEMI demonstrates that circulating levels of IL-6, soluble tumor necrosis factor receptor type I, and the neutrophil-to-lymphocyte ratio are significantly elevated in older individuals within the first 48 hours post-onset compared with younger cohorts, highlighting an exacerbated post-infarction inflammatory response [166]. Furthermore, advancing age promotes a macrophage polarization bias toward the pro-inflammatory M1 phenotype, perpetuating a chronic inflammatory state that severely compromises tissue repair [167]. Collectively, acute or chronic aging-related immune perturbations

triggered by ischemic insults may profoundly influence the progression of atherosclerosis, a critical mechanistic link that warrants further investigation.

Treatment strategies

Emerging therapeutic strategies to prevent accelerated atherosclerotic plaque progression following acute ischemic events are grounded in a deeper understanding of immune and vascular mechanisms [10, 168]. A promising approach focuses on modulating the adaptive immune response. Targeting B and T cell activities through antigen-specific immunotherapy, such as anti-CD20 antibodies or vaccines designed to stimulate protective IgM responses against oxidized phospholipids, offers potential in mice for mitigating the chronic inflammatory environment that contributes to accelerated plaque progression [169, 170]. Simultaneously, efforts to reduce the recruitment of proinflammatory monocyte subsets have shown promise. For instance, pharmacological inhibition of chemokine receptors like CCR2, CCR5, or CX3CR1 has been linked to reduced Ly-6C^{hi} monocyte accumulation in murine atherosclerosis models and human plaque data, thereby limiting their differentiation into macrophages within plaques [171, 172]. Beyond its lipid-lowering effects, statin therapy has proven effective in reducing hypercholesterolemia-induced monocytosis, particularly within the Ly-6C^{hi} subset, in murine MI models, suggesting an additional anti-inflammatory benefit [173, 174].

Interventions aimed at reperfusion injury also play a role in limiting plaque destabilization. Approaches such as left ventricular unloading and oxygen supersaturation in patients with myocardial infarction have been evaluated for their capacity to reduce infarct size and alleviate microvascular obstruction, thereby mitigating subsequent atherosclerotic progression [175–177]. Randomized controlled trials have highlighted low-dose colchicine as an effective treatment for reducing cardiovascular event rates in patients with chronic coronary disease, highlighting the significant role of inflammation in accelerated plaque progression [178, 179]. Additionally, preclinical studies suggest that modulating monocyte differentiation—specifically the balance between early inflammatory Ly-6C^{hi} and later reparative Ly-6C^{low} populations—can enhance infarct healing and prevent maladaptive ventricular remodeling [73].

StemBell therapy not only modulates the local inflammatory response after MI but also enhances plaque stability by altering immune cell composition and the distribution of chemokines both within and around the plaque [180, 181]. This therapy combines adipose-derived mesenchymal stromal cells (ASCs) with dual-targeted microbubbles, which, when activated by ultrasound, direct the cells to the MI and atherosclerotic plaque regions, thereby stabilizing the plaques[180]. In the experiment, an ApoE$^{-/-}$ mouse model was employed, with MI induced after six days of a high-fat diet. On day six post-MI, StemBells were administered intravenously, followed by ultrasound exposure to efficiently target the damaged area[180]. Twenty-eight days later, the results indicated that although the size of plaques in the StemBell-treated group remained largely unchanged, their fibrous caps were significantly thickened, suggesting plaque stabilization[180]. Concurrently, a reduction in inflammatory cells within the plaques was observed, particularly a 51% decrease in Mac3-positive macrophages, while the proportion of anti-inflammatory CD163-positive macrophages nearly doubled[180]. Furthermore, the pro-inflammatory chemokine monocyte chemoattractant protein-1 (MCP-1) was reduced in plaques, whereas the level of CX3CL-1, which attracts anti-inflammatory nonclassical monocytes, was elevated[180]. These changes collectively contributed to the formation of an inflammation-reducing microenvironment, promoting plaque stabilization.

In the area of MI, StemBell therapy similarly induced an increase in anti-inflammatory macrophages while reducing the number of mast cells in the heart, demonstrating a local immunomodulatory effect [182]. Blood tests, in contrast, showed an upward trend in the proportion of anti-inflammatory monocytes in murine circulation following StemBell therapy [183, 184]. Importantly, this treatment did not impact serum cholesterol and triglyceride levels or overall plaque volume; its primary mechanism of action was the modulation of local and systemic immune-inflammatory responses, promotion of immune cell polarization toward an anti-inflammatory phenotype, and stabilization of plaque structure [185].

Together, these therapeutic approaches provide an entry point for targeting distinct aspects of the pathological continuum initiated by acute ischemic events. Immune modulation, whether through adaptive or innate mechanisms, along with the reduction of reperfusion injury, plays an essential role in diminishing the inflammatory burden and preventing plaque destabilization. This integrated strategy presents a promising direction for the development of targeted therapies aimed at reducing recurrent ischemic events in atherosclerotic patients. However, these therapeutic strategies have thus far been validated solely in animal models or *in vitro* assays, and whether they can translate into clinical efficacy in patients remains to be established through further investigation.

Table 3. Classification of Evidence Supporting Mechanisms of Accelerated Atherosclerosis Following Acute Ischemic Events.

Study/Author	Study Type	Key Findings	Ref.
Jernberg et al. (2015)	Retrospective cohort study	Provided robust epidemiological evidence of persistently elevated long-term risk for recurrent ischemic events post-MI.	[20]
Thune et al. (2014)	Prospective cohort study	Demonstrated that a recurrent myocardial infarction in high-risk patients (with left ventricular dysfunction or heart failure) exponentially increases both short- and long-term mortality, highlighting the severe prognostic impact of secondary ischemic events despite contemporary treatments.	[21]
Ozawa et al. (2023)	Animal MI models	Showed that elevated LDL cholesterol exacerbates post-MI microvascular thromboinflammation via excess endothelial VWF and platelet adhesion, linking lipid burden to impaired microvascular reflow, larger infarct size, and late adverse ventricular remodeling.	[28]
Schnitzler et al. (2020)	Biomarker study	Revealed that Lp(a) and its oxidized phospholipids activate arterial ECs by upregulating PFKFB3-mediated glycolysis, driving a pro-inflammatory state that facilitates monocyte transmigration into the vessel wall.	[36]
Swirski et al. (2009)	Animal MI models	Identified the spleen as a major reservoir of undifferentiated monocytes that are rapidly mobilized to inflammatory sites following myocardial infarction through Angiotensin II-AT-1 receptor signaling.	[53]
Flores-Gomez et al. (2020)	Animal MI models	Outlined how endogenous atherogenic stimuli induce metabolic and epigenetic trained immunity, sustaining chronic atherosclerotic inflammation.	[66]
Li et al. (2017)	Animal stroke models	Demonstrated that hyperglycemia induces persistent epigenetic trained immunity in macrophage precursors, accelerating atherosclerosis despite glucose normalization.	[75]
Guerin et al. (2017)	Prospective cohort study	Demonstrated that an elevated serum cholesterol efflux capacity is a strong, independent predictor of improved long-term survival in patients following acute myocardial infarction, independent of static HDL cholesterol levels.	[77]
Joshi et al. (2015)	Prospective cohort study	Demonstrated via 18F-FDG PET-CT that MI triggers a systemic inflammatory response, increasing metabolic activity in remote aortic atherosclerotic plaques proportional to the infarct size. Clinically, larger infarct size independently predicts a significantly higher risk of early recurrent MI (within 30 days).	[92]
Loftus et al. (2000)	Carotid endarterectomy samples	The concentration, production, and expression of MMP-9 is significantly increased in unstable carotid plaques. If this proves to be a causal relationship, MMP-9 may be a strong candidate for pharmacotherapy aimed at stabilizing plaques and preventing stroke.	[129]

Abbreviations: MI, myocardial infarction; AT1R, angiotensin II type 1 receptor; SYK, spleen tyrosine kinase; KMT5A, lysine methyltransferase 5A; STEMI, ST-segment elevation myocardial infarction; LDL, low-density lipoprotein; HDL, high-density lipoprotein; PET-CT, positron emission tomography-computed tomography; MMP-9, matrix metalloproteinase-9.

Conclusion

While the immediate management of acute ischemic events has advanced, this review synthesizes evidence that these events function as active catalysts. They trigger a systemic, multi-modal reprogramming of the host's biological landscape, rather than serving as merely transient, passive stressors. Preclinical data robustly implicate the sympathetic-monocyte axis and trained immunity as primary drivers of accelerated atherosclerosis, yet a critical uncertainty remains regarding the biological weight of these pathways in human cohorts compared to traditional risk factors, such as LDL cholesterol. Furthermore, a pivotal insight emerges from the convergence of ischemia with biological aging; mechanisms such as Notch1-mediated

endothelial senescence and HMGB1-RAGE-driven inflammation suggest that an acute event can precipitate vascular aging, effectively compressing years of senescence into weeks. For the elderly, this implies that secondary prevention must evolve beyond lipid-lowering to address pro-inflammatory milieu and the exhaustion of bone marrow-derived EPCs.

Future research must transition from broad evidence synthesis toward testable, mechanism-driven intervention strategies to disrupt the vicious cycle of accelerated plaque progression. Several critical avenues warrant priority investigation. First, pharmacological inhibition of HK2 to reprogram monocyte glycolysis represents a promising therapeutic approach for suppressing systemic inflammation without disrupting overall glucose homeostasis. Second, future work must elucidate the intracellular signaling cascades downstream of the VWF–GPIbα axis, specifically defining how these signals traverse intercellular barriers to precisely and selectively induce MMP-9 zymogen activation or transcriptional upregulation within macrophages and smooth muscle cells. Third, given the complex alarmin milieu (e.g., HMGB1, hsp60, mtDNA) released by the injured myocardium following MI, it is crucial to identify the cardinal drivers of B-cell activation and evaluate whether selective neutralization of an individual alarmin can effectively abrogate the humoral immune response that exacerbates atherosclerosis. Finally, while emerging immunomodulatory strategies—such as StemBell cell therapy or chemokine receptor targeting—hold promise for plaque stabilization by promoting anti-inflammatory macrophage polarization and fibrous cap thickening independently of lipid lowering, they encounter substantial translational bottlenecks. Chiefly, researchers must resolve the dichotomy between targeted therapy and systemic immunosuppression: how to effectively curb pro-inflammatory monocyte infiltration, clear senescent cells, and interrupt the pathological feedback loops driven by CHIP, while avoiding heightened infection risks or the impairment of physiological repair mechanisms within the cardiovascular system. Ultimately, shifting the clinical paradigm from regarding myocardial infarction and stroke as terminal events to recognizing them as systemic catalysts for progressive vascular deterioration is imperative for the optimization of long-term patient outcomes.

Author contributions

Jie-hong Wu and Bo Hu: Conceptualization, Funding acquisition, Supervision, Writing - review & editing. Jiang-ming Yu and Yu-Xiao Liu: Conceptualization, Writing - original draft, Writing - review & editing, visualization. Qin Li: Conceptualization, Writing - review & editing. Jia-Bin Zong, Tuersun Aili and Xin-Ran Zhao: Writing - review & editing.

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Competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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